competency, and that definition has been widely accepted; and (c) Applicant has defined the term in the specification without reference to germ-line-competency and is entitled to act as his own lexicographer in this application.

(a) The Office Action relies on the Nichols et al. reference for a purported definition of embryonic stem cells which requires germ-line-competence. Nichols et al. said nothing about what the term means in the context of human embryonic stem cells. It related to mouse embryonic stem cells.

Even in the context of mouse embryonic stem cells the Nichols et al. reference did not define the term as including germ-line-competency. In fact, the title of the Nichols et al. article used the term "germ-line-competent embryonic stem (ES) cells". If the definition of embryonic stem cell in the mouse already included germ-line-competency, there would be no reason to use the words "germ-line-competent" in the title.

Further, the first sentence of the introduction of Nichols et al. defined mouse ES cells as "permanent cell lines established directly from the inner cell mass of the pre-implantation mouse embryo" citing the definition of Martin (who coined the term as applied to the mouse). We enclose herewith a copy of the Martin article, G. Martin, 78 P.N.A.S. USA 7634-7638 (1981). Martin specifically noted on page 7635 her rationale for why she chose the term:

> Such cells were termed embryonic stem cells (ESC) to denote their origin directly from embryos and to distinguish them from embryonal carcinoma cells (ECC)...

There is no assertion in the Martin article of germ-line-competence, or anything in the specified Martin definition to require this attribute, and we are not aware of the Martin line ever having been reported to have this feature.

The Office Action apparently relies mostly on the next two sentences of the introduction of Nichols et al. which state that:

> They retain the ability to participate in normal embryonic development and, following reintroduction

> to the blastocyst, they generate chimaeric animals that are mosaic in all their tissues. Mosaicism extends to the germ cell lineage and ES cells can contribute fully functional gametes (Bradley et al. 1984).

However, this was not an attempt to redefine what an ES cell is. It was merely a recognition that Bradley et al. had developed a mouse line which had this attribute. This can be better understood by comparing the discussion at page 1347 of the Nichols et al. article, column 1, where it was acknowledged that:

> Other workers have reported that not all ES lines differentiate normally and relatively few exhibit high levels of germ-line transmission [citing other Martin articles]

Thus, contrary to what it is cited for, Nichols et al. does not purport to redefine what a mouse embryonic stem cell is, and it notes that most mouse embryonic stem cells are poor in germ line transmission.

(b) In J. Thomson et al., 282 Science 1145-1147 (1998), a peer reviewed publication, the term "human embryonic stem cell" was coined. Note the specific recitation in that article that germ-line-competence is not a required attribute. This definition was accepted by the publisher and the peer review committee, and this is prima facie evidence that the term is not repugnant to an accepted definition in the art.

Moreover, the art has widely accepted the Thomson definition. See e.g. J. Rossant et al., 17 Nature Biotechnology 23-24 (1999); J. Gearhart, 282 Science 1061-1062 (1998); A. Chapman et al., Stem Cell Research And Applications Monitoring The Frontiers Of Biomedical Research, American Association for the Advancement of Science and Institute for Civil Society (November, 1999). For example, at page 24 of the Rossant et al. article, the following appears:

> Given that the ultimate test of a true ES cell -- the ability to contribute to all cell types, including the germ line, in a chimera -- is not applicable to humans for ethical and practical reasons, the properties reported so far for these human cells suggest that they are indeed pluripotent embryonic stem cells. [emphasis added]

Thus, the Office Action does not meet a prima facie burden of establishing that in the context of a human embryonic stem cell there is a widely accepted definition which requires germ-line-competency for a cell line to be a human embryonic stem cell. Moreover, it clearly does not establish that the art would find Applicant's definition unacceptable or repugnant.

(c) M.P.E.P. § 2173.01 states:

> A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art.

At page 7, beginning line 10 of the specification, a definition of ES cells is provided. No mention is made of germ-line-competency. Applicant is entitled to use this definition because (as noted above) it is not contrary to a well accepted meaning in the art for human embryonic stem cells.

Interview Summary

After discussing the above (and also the ethical and legal concerns that conducting experiments to create recombinant humans would raise), Examiner Deborah Clark and SPE John LeGuyader indicated that there was sufficient merit in these arguments to permit further consideration (albeit no agreement was reached at this point). They indicated that they would need to consult with the group director (who was not involved in the interview) regarding these issues.

Conclusion

In view of the above Remarks and enclosed Submissions, the application is now believed to be in condition for allowance, and allowance is respectfully requested. No additional fee is believed necessary with respect to this Amendment. However, if one is, please charge deposit account

17-0055 for the amount of the fee.

Respectfully submitted,

James A. Thomson

Dated: March 13, 2000 By: _____

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